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Triflic acid and its derivatives

A family of useful reagents for synthesis

INTRODUCTION

Trifluoromethane sulfonic acid ($\text{CF}_3\text{SO}_3\text{H}$), also known as triflic acid, is one of the strongest Brønsted acids, with a pK_a of -13.6 (1). It is one of a small group of acids commonly known as "super acids", being stronger than 100% sulfuric acid. Amongst this special class of compounds, triflic acid has several important advantages. It is non-oxidizing, has a high thermal stability, is resistant to both oxidation and reduction, and does not yield fluoride ions, even in the presence of strong nucleophiles (2). Unlike sulfuric acid, fluorosulfuric acid or chlorosulfuric acid, it does not lead to sulfonations and can be used in various protonation reactions. This novel collection of properties has made triflic acid an important reagent and catalyst in modern synthetic chemistry. As a comparatively new substance – it was first reported in 1954 (3) and subsequently commercialized (4) – researchers continue to find new and interesting applications of triflic acid.

This review is intended to summarize the previous literature on triflic acid, triflic anhydride and simple salts and esters and to highlight certain applications to fine chemical and pharmaceutical synthesis. The reader is referred to several excellent review articles that have previously appeared on this subject (2,5,6).

TRIFLIC ACID

Preparation

Triflic acid was first reported from the oxidation of bis(trifluoromethylthio)mercury (3). The commercial production is by electrochemical fluorination (ECF) (4) although recent reports of a new synthetic route have appeared (7). Laboratory quantities can be obtained by the basic hydrolysis of $\text{CF}_3\text{SO}_2\text{F}$ followed by acidification (3,8). It is commercially available from several suppliers.

Properties

Pure triflic acid is a clear, colorless liquid that fumes in moist air. It forms a stable monohydrate which is a solid at room temperature (m.p. 34°C) (9). It is miscible in all proportions with water and soluble in many organic solvents, including dimethylformamide, dimethylsulfoxide, sulfolane, and acetonitrile. Although it is soluble in various alcohols, ketones, ethers, esters and acids, the solutions are generally not inert. The properties of triflic acid are summarized in Table I.

Because of the hygroscopic nature of triflic acid, handling and transfer under a dry, inert atmosphere is recommended. Contact with natural and most synthetic

polymers (rubber, cork, common plastics) can lead to reaction. For this reason, storage in glass or PTFE containers is recommended.

Reactions

Friedel-Crafts Alkylation and Acylation

Strong Brønsted acids such as sulfuric acid have been traditionally used for hydrocarbon conversions and alkylation in the preparation of high octane gasoline (10). Triflic acid has been demonstrated to be effective in the production of alkylates (11). The combination of triflic acid and antimony pentafluoride has been shown to prepare high octane alkylates (12). Para-substituted phenols react with two moles of isobutylene in the presence of catalytic amounts of triflic acid to make 2,6-di(*t*-butyl)-4-substituted phenols (13).

Acylation reactions using triflic acid have also been well studied. Catalytic amounts of triflic acid are generally sufficient to achieve high yields of acylated product (14), offering an environmental advantage over the use of large excesses of anhydrous aluminum chloride.

Polymerization of Olefins

Triflic acid has been extensively investigated as a catalyst for the polymerization of such olefins as styrene, substituted styrenes and butadienes (2). With styrene, the linear dimer, trans-1,3-diphenyl-1-butene is selectively formed (15).

Polymerization of Ethers and Siloxanes

Tetrahydrofuran is readily polymerized by catalytic amounts of triflic acid to give either cyclic or straight chain polyethers (16,17). Cyclic acetals such as trioxane,

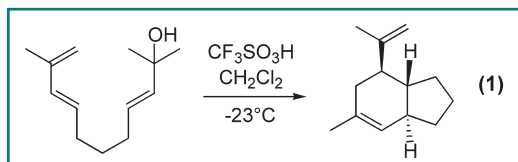
Property	Value
CAS #	1493-13-6
Formula weight	150.08
Melting point	-40°C
Boiling point	162°C
Vapor density (air = 1)	5.2
Vapor pressure at 20°C	8 mm Hg
Specific gravity (g/ml)	1.696
Refractive Index (at 25°C)	1.325
Flash point	Nonflammable
Toxicity LD50 (oral-rat)	1605 mg/kg
Viscosity (at 25°C)	2.87 cP
Electrical conductivity (at 25°C)	$2 \times 10^{-4} \Omega^{-1} \text{cm}^{-1}$
Solubility in water	Miscible in all proportions
Solubility in organic solvents	DMF, DMSO, acetonitrile

Table I - Properties of triflic acid

1,3-dioxolane, and 2,2-dimethyl-1,3-dioxolane can be homopolymerized or co-polymerized with triflic acid (18). Siloxanes are likewise polymerized to polysiloxanes (19,20).

Diels-Alder Reactions

The strong protonating power of triflic acid can be used to generate allyl cations suitable for low temperature ionic Diels-Alder reactions. A highly stereoselective example is given in Equation 1 (21).

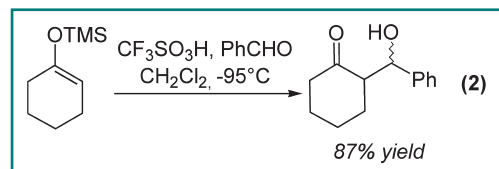


Hydrogenation of Alkenes

The use of triflic acid with a hydride donor such as triethylsilane can give high yields of hydrogenated olefins. Even tetrasubstituted alkenes can be reduced to alkanes (22).

Aldol Condensations

Aldehydes and acetals can be condensed with silyl enol ethers using triflic acid – see for example Equation 2 (23).

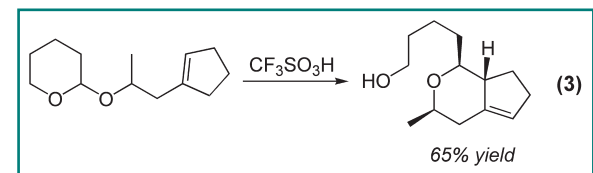


Deblocking Reactions

Triflic acid is effective in the rapid and quantitative cleavage of acid-labile amino protecting groups (24,25).

Cyclizations

Cyclization of 3- and 4-arylalkanoic acids to bicyclic ketones, via the corresponding acid chlorides, can be carried out in high yield with triflic acid (26). Another particularly elegant stereocontrolled cyclization is shown in Equation 3 (27).



Commercial Aspects

Research quantities of up to 5 kg of triflic acid are available from a number of laboratory reagent suppliers. These are commonly packaged in glass containers, either sealed ampules or closed with a PTFE cap. Commercial quantities are packaged in stainless steel drums, net 10, 50 or 90 kg. Most suppliers offer two grades, standard and high purity. Typical specifications are given in Table II.

For transportation purposes, triflic acid is classified as a corrosive liquid, acidic, organic N.O.S., hazard class 8, packing group I.

Specification	Standard Grade	High Purity Grade
Appearance	Colorless liquid	Colorless liquid
Purity	99.5 wt. % min	99.9 wt. % min.
Free Fluorine	10 ppm max.	2 ppm max.
Water	500 ppm max.	300 ppm max.
Sulfate	50 ppm max.	10 ppm max.

Table II - Specifications of commercial grade triflic acid.
Data courtesy of Central Glass International, Inc.

It carries a corrosive label and ID number UN 3265. It is listed on the Toxic Substances Control Act (TSCA) inventory list of the U.S. Environmental Protection Agency. It is recommended to store the product in its original, unopened container, in a cool, well-ventilated area.

TRIFLIC ANHYDRIDE

Preparation

Triflic anhydride can be prepared by the careful distillation from a mixture of triflic acid and phosphorus pentoxide (9,28,50).

It is commercially available from manufacturers of triflic acid.

Properties

Triflic anhydride is a colorless liquid that hydrolyzes on exposure to water to give triflic acid. The properties are summarized in Table III.

Table III - Properties of triflic anhydride

Property	Value
CAS #	358-23-6
Formula weight	282.13
Melting point	-80 °C
Boiling point	83-84 °C
Specific gravity (g/ml)	1.68
Refractive index (at 25°C)	1.3210
Flash point	None
Solubility in water	Reacts

Reactions

Esterification

A wide variety of esters of triflic acid can be prepared by reaction of the corresponding anhydrous alcohol with a slight excess of triflic anhydride in pyridine as a solvent (6,9). Alkyl triflates are useful intermediates for a range of nucleophilic substitution reactions as the triflate group is an excellent leaving group (28).

Amination

Anhydrous ammonia reacts with triflic anhydride to give trifluoromethanesulfonamide. Other amines react at a 1:1 molar ratio in a similar manner to give the corresponding triflamides (9,29). If two moles of triflic anhydride are used, triflimides are formed. Triflamides are readily alkylated to give dialkyltriflimides.

Reaction with Carbonyl Compounds

Enolizable ketones react with triflic anhydride to give the corresponding vinyl triflate. These can serve as the starting point for a broad range of synthetic reactions. Enol triflates have been extensively reviewed (2, 30-32).

SILYL TRIFLATE ESTERS

Preparation

Trimethylsilyl triflate, also known as TMS triflate, can be prepared by the reaction of triflic acid with chlorotrimethylsilane (33) or by the protodesilylation of phenyltrimethylsilane (34). It is one of the most widely used silylating reagents, far superior to chlorotrimethylsilane (35).

Other silyl triflate esters have also been prepared.

Properties

Trimethylsilyl triflate is a colorless, moisture sensitive liquid, soluble in aliphatic and aromatic hydrocarbons, haloalkanes and ethers. It is flammable and corrosive (36).

Reactions

Carbonyl compounds with α -hydrogens give silyl enol ethers on treatment with trimethylsilyl triflate (37,38). In general C-silylation predominates over O-silylation (39). Aliphatic ethers do not react with TMS triflate and benzyl ethers are inert under the same conditions (40). The use of TMS triflate in aldol reactions of silyl enol ethers and ketene acetals with aldehydes is ubiquitous (41). TMS triflate also activates many selective glycosidation reactions (42).

TRIFLATE SALTS

More than twenty metal salts of triflic acid have been reported in the literature. Their use as catalysts and reagents is an important and growing area of modern synthetic chemistry, particularly in fine chemical synthesis. Examples include the preparation of C-glucosides using silver triflate (43,44) or tin(II) triflate (45,46) and the cyclization of β -amino thiol esters to cis- β -lactams with copper(I) triflate (47). The strong Lewis acidity of bismuth (III) triflate has recently been reviewed (48). A survey of the chemistry of metal triflates is under preparation by the author (49). Table IV lists selected metal triflate salts that are commercially available, either in research quantities or in bulk.

Compound	CAS #
Aluminum triflate	74974-61-1
Ammonium triflate	38542-94-8
Barium triflate	2794-60-7
Bismuth (III) triflate	
Calcium triflate	55120-75-7
Copper (I) triflate-toluene complex	48209-28-5
Copper (II) triflate	13454-88-1
Indium (III) triflate	128008-30-0
Lanthanum (III) triflate	52093-26-2
Lithium triflate	33454-82-9
Magnesium triflate	60871-83-2
Potassium triflate	2926-27-4
Scandium (III) triflate	144026-79-9
Silver (I) triflate	2923-28-6
Sodium triflate	2926-30-9
Tin (II) triflate	62086-04-8
Ytterbium (III) triflate	54761-04-5
Zinc triflate	54010-75-2

Table IV - Selected salts of triflic acid

CONCLUSION

As we approach the 50th anniversary of the first preparation of triflic acid, it is remarkable to see how extensively the chemistry of this novel compound has been explored. New discoveries and applications continue to be made in both industrial and academic laboratories. Triflic acid and triflic anhydride (50) promise to have an important and exciting future.

ACKNOWLEDGMENTS

The author gratefully acknowledges the helpful assistance of SynQuest Laboratories and Central Glass International

in the preparation of this article.

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